Parental occupational exposures and the risk of cerebral palsy in children

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Abstract
Introduction: Association of parental occupational exposure to chemicals with cerebral palsy (CP) in children remains poorly characterized.

Objectives: To ascertain the role of parents' occupational exposure in CP in children in major Kazakhstan cities using a case-control design.

Method: We enrolled 150 cases, including children one month to 18 years old, and 150 controls in all regions of Kazakhstan. Cases were children with confirmed diagnoses on treatment or rehabilitation, whereas controls were their counterparts with no CP. Exposure to hazardous chemicals of parents at work and other demographics were collected with structured questionnaires, and logistic regression models, crude and adjusted, were used to calculate the odds of CP in children, expressed as odds ratios (OR) with their 95% confidence intervals (CI).

Results: Most cases (52%) were children below one year of age. Prevalence of parents' alcohol use did not differ between the groups, whereas we found more smokers in parents of controls compared to cases. There were more fathers in cases with exposure to chemicals (21% vs. 5% in controls, p<0.001). Father's occupational chemical exposure increased the odds of CP in children (OR 18.7 (95% CI 3.3; 105.7), adjusted for age, sex, father's highest attained education and mother's education; and OR 36.8 (95% CI 3.6; 370.5) if further adjusted for father's and mother's smoking).

Conclusions: Father's occupational chemical exposure increased the odds of CP in children (OR 18.7 (95% CI 3.3; 105.7), adjusted for age, sex, father's highest attained education and mother's education

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Introduction
The prevalence of cerebral palsy (CP) may range depending on age, and the polled estimate from meta-analysis was 2.1 per 1000 live births[1]. A wide range of risk factors for CP have been studied and reported. In China, a study showed that the prevalence of CP in multiple births was 9.7 per 1000 children, 6.5 times that in singletons[2]. Genetic factors, such as genetic polymorphism of *NOS1* gene[3] and environmental factors, such as exposure to methyl mercury during pregnancy, iodine deficiency[4] and even high blood lead levels[5] may be important, but perinatal causes remain the leading cause of CP[6], especially small for gestational age[7]. Caesarean delivery was believed to be associated with CP, but a systematic review found no association[8].

Environmental factors and their potential for CP attract attention, since a huge fraction of population still resides in polluted cities, and the level of chemical exposure is growing, especially in developing nations. A recent study in China showed that father's occupational exposure increased the risk 3-fold[9]. In Kazakhstan, noted for high level of environmental pollution in major cities and occupational exposure from the remaining industry, these environmental contributors may play a role, but no analysis was published from Kazakhstan in the recent years.

Objectives
To ascertain the role of parents' occupational exposure in the greater likelihood of CP in children in the major Kazakhstan cities using a case-control design.

Method
This was a case-control study of the association of occupational exposure of either of the parents with CP in children. Cases were children of one month to 18 years old, identified by the medical personnel of the charity organization, which is actively involved in rehabilitation of children with CP in all regions of Kazakhstan. These cases were all with confirmed diagnoses, all on the state register and receiving rehabilitation. Neurological deficit was different in cases, as was the functional status of selected motor activities. The study protocol was

approved by the Local Committee on Bioethics of the Kazakh Medical University of Continuing Education (Minutes #1 dated September 20, 2017).

In total, we enrolled 150 cases with 150 controls using 1:1 ratio. For sample size calculation, we use data from the previous study where they reported occupational exposure of fathers[9]. Although we tried to enroll subjects from all regions of Kazakhstan, the sample was mostly constructed from residents of the largest city, Almaty along with the province surrounding it (Table 1).

Table 1: *The distribution of cases and controls from the regions within the country*

	Cases Number (%)	Controls Number (%)	Total Number (%)
No answer	13 (09)	0 (0)	13 (04)
Almaty	33 (22)	90 (60)	123 (41)
Astana	17 (11)	01 (01)	18 (06)
Aktubinsk province	38 (25)	0 (0)	38 (13)
Akmola province	23 (15)	0 (0)	23 (08)
Almaty province	19 (13)	54 (36)	73 (24)
Atyrau province	04 (03)	0 (0)	04 (01)
East Kazakhstan province	01 (01)	0 (0)	01 (0)
Jambyl province	0 (0)	0 (0)	0 (0)
Karaganda province	0 (0)	02 (01)	02 (01)
Kostanay province	0 (0)	0 (0)	0 (0)
Kyzylorda province	0 (0)	01 (01)	01 (0)
Mangystau province	0 (0)	0 (0)	0 (0)
Pavlodar province	01 (01)	0 (0)	01 (0)
North Kazakhstan province	0 (0)	01 (01)	01 (0)
South Kazakhstan province	01 (01)	0 (0)	01 (0)

Exposure was ascertained using a structured questionnaire, which was offered to each child's mother and consisted of 150 questions covering demographics of a child and parents as well as parents' lifestyle and occupational and environmental exposures. Demographic part included questions on sex, age, place of birth and place of current residence, ethnic origin, family composition at a time of birth and at a time of survey, and highest attained education of father and mother. We then asked whether any parent was a smoker some time before delivery or used any alcohol for some time before delivery. Finally, this part of the questionnaire contained questions on the age of mother and father at a time of child's birth. Occupational history contained two questions separately for each parent, including the one whether he/she was exposed to chemical, biological or physical occupational factors for at least one year and whether his/her workplace were enlisted as unfavourable for the state regulatory bodies. Should they answer 'yes' to the first occupational question, they were asked to categorize exposure to chemical, biological of physical.

We analysed both continuous and binary data in this report. Data were tested for normality and should this be confirmed, cases were compared to controls using t-test, or Mann-Whitney U-test as an alternative. Binary data were tested using χ^2 test. In the univariate analysis, we calculated odds ratios (OR) with their corresponding 95% confidence intervals (CI). In case of $p<0.05$ in the univariate comparisons, we also applied multiple logistic regression to adjust for potential confounding, however, only those variables were treated as confounders if it was considered plausible to place a potential confounder of a causal pathway from the exposure to the outcome in the directed acyclic graph (DAG) analysis. We performed all calculations using NCSS12 (Utah, USA), and p-values below 0.05 were considered significant (type 1 error below 5%).

Results
Most cases were children below one year of age, whereas controls were mostly teenagers (Table 2). We also found significant differences in most included variables related to family composition and educational levels of parents. Thus, there were significantly more boys, not full families (one parent only) and families with more children in CP group compared to controls. With regard to parents' educational levels, CP children were more likely to be born in families with smaller likelihood of either parents to have a university degree.

Table 2: *Univariate analysis of baseline demographic variables and other confounders*

Variable	Cases Number (%)	Controls Number (%)	p-value
Age			
29 days-<1 year	78 (52)	03 (02)	
1-3 years	45 (30)	18 (12)	
4-6 years	04 (03)	24 (16)	0.001
7-11 years	11 (07)	52 (16)	
12-18 years	12 (08)	53 (35)	
Sex			
Male	85 (57)	61 (41)	0.01
Female	65 (43)	89 (59)	
Ethnicity			
Kazakh	89 (53)	73 (49)	
Russian	35 (23)	40 (37)	0.14
Other	26 (17)	37 (25)	
Family composition			
1 kid	53 (35)	81 (54)	
2 kids	42 (28)	66 (44)	
3 kids	33 (22)	03 (02)	0.001
4 kids	14 (09)	0 (0)	
5 kids or more	08 (05)	0 (0)	
Family			
Full	98 (65)	146 (97)	0.001
Not full	52 (35)	04 (03)	
Mother's highest attained education			
None	0 (0)	45 (30)	
High school	25 (17)	04 (03)	0.001
College	116 (77)	78 (52)	
University	10 (07)	23 (15)	
Father's highest attained education			
None	01 (01)	46 (31)	
High school	39 (26)	0 (0)	0.001
College	100 (67)	77 (51)	
University	10 (07)	27 (18)	

*Note: p-values are from χ2 tests from 2*X tables, where X – count rows.*

With regard to self-reported addictions and lifestyle attributes, such as smoking and alcohol, bivariate analysis failed to confirm the association of alcohol use in parents with the likelihood of CP in children (Table 3). In both groups, alcohol use prevalence in fathers was quite high, reaching 70% in families where CP were born. On the contrary, smoking was far less prevalent in both groups. In addition, both parents were much more likely to smoke in families with healthy children, reflecting greater number of parents with no education at all in the control groups. Occupational chemical exposure of father, as opposed to the one of mother, was associated with greater odds of having a CP child (OR 19.3 (95% CI 4.5; 82.2)). The use of an alternative classification of occupational exposure, such as working on a position at any time, classified as hazardous, yielded positive association for both father and mother (Table 3). The table shows that 61% of mothers having CP child were employed in such workplaces, as opposed to only 1% of mother heaving healthy children. Somewhat similar association was found when father jobs were considered.

Table 3: Smoking, alcohol and occupational exposures of parents in cases compared to controls

Variable	Cases Number (%)	Controls Number (%)	p-value
Mother's smoking			
Yes	01 (01)	56 (37)	0.001
No	149 (99)	94 (63)	
Father's smoking			
Yes	43 (29)	90 (60)	0.001
No	107 (71)	60 (40)	
Mother's alcohol			
Yes	15 (10)	23 (15)	0.16
No	135 (90)	127 (85)	
Father's alcohol			
Yes	105 (70)	95 (63)	0.22
No	45 (30)	55 (37)	
Mother's occupational chemical exposure			
Yes	51 (34)	52 (35)	0.90
No	99 (66)	98 (65)	
Father's occupational chemical exposure			
Yes	32 (21)	07 (05)	0.001
No	118 (79)	143 (95)	
Mother's classified hazardous job			
No	58 (39)	149 (99)	0.001
Yes	92 (61)	01 (01)	
Father's classified hazardous job			
No	30 (20)	150 (100)	0.001
Yes	120 (80)	0 (0)	

Age, sex and the highest attained education of both parents differed between the groups in the bivariate analyses, therefore, they were included in the models as confounders on the pathway between the occupational exposure of parents and the odds of having a CP child. Model 1 in Table 4 shows that father's occupational chemical exposure in adjusted models increased the likelihood 18.7-fold. Mother's hazardous job was a very strong predictor of having a child with CP with a very strong association in an adjusted model. Because smoking of either parent can have an association with the likelihood of high occupational exposure, we considered smoking as an important confounder on a pathway between parents' occupational exposure and CP in their children. Therefore, we additionally adjusted the models with smoking status of both parents. Table 4 demonstrates that adjustment for smoking status resulted in even a stronger effect of father's occupational exposure on a chance of having a child with CP. Adjustment for smoking in mother reduced the effect, reflecting on the correlation between mother's smoking and the chance of having a hazardous job. Overall, both father's occupational chemical exposure (OR 36.8 (95% CI 3.6; 370.5)) and mother's hazardous job (OR 86.1 (95% CI 9.0; 828.0)) were very strong predictors of CP in their children.

Table 4: Regression analysis of selected predictors for CP in cases and controls

	Crude OR	Model 1	Model 2
Father's occupational chemical exposure	19.3 (4.5;82.2)	18.7 (3.3;105.7)	36.8 (3.6;370.5)
Mother's classified hazardous job	236.3 (32.2;1375.6)	118.7 (15.1;930.9)	86.1 (9.0;828.0)
Father's classified hazardous job	Unstable model	Unstable model	Unstable model

Note: OR – odds ratio; Model 1 adjusted for age, sex, father's highest attained education and mother's education; Model 2 adjusted for age, sex, father's highest attained education, mother's education, father's smoking and mother's smoking.

Discussion

This is the first presentation from Kazakhstan on the occupational exposure of parents as a risk factor for CP in their children. In this case-control study we found a very high risk of CP in children when either father was exposed to chemicals at work or mother was employed in a hazardous workplace.

Compared to few other studies on such association, the effect in the current study appears to be very strong even in adjusted models. Taken together, this necessitates improved counseling in those planning to have children in the near future as well as planning and implementation of wider studies with better exposure assessment in order to determine which specific occupational exposures may be attributable to the risk.

Existing evidence on the potential association of CP with parents' occupational exposure is very scarce. Chinese paper is one of very few[9], if any, to highlight 3-fold increase in the risk, whereas other presentations on CP risk factors do not focus on the occupational causes at all. Because epidemiological evidence is insufficient, speculations over the biological plausibility did not attract much attention so far. The nature of such occupational exposure likely plays a role, because the range of potential hazardous substances and their effects may be too wide. The current analysis showing that 21% of fathers of CP children vs. 5% of fathers in controls taken together with very high prevalence of hazardous jobs in mothers in CP group resulted in very high ORs of the disease with wide 95% confidence intervals. Apparently, these exposures are important to induce or promote pathology entailing CP in children, but the effect measures have to be confirmed in other populations.

Our study has a number of strengths including sufficient statistical power resulting from the sample size, inclusion of children from all provinces of Kazakhstan, and the use of detailed questionnaire for parents ascertaining parental risk factors. However, a number of limitations should also be noted. First and most important was some potential for exposure misclassification. We did not obtain detailed work history of each parent from their employers or other reliable sources and used self-reported information instead. No job-exposure matrix was used in this analysis for exposure classification. Moreover, we had to limit occupational history collection to 4 questions only covering a very broad range of potential chemical exposures. With the evidence evolving from our study on a strong association of parental occupational exposure with CP in children, future studies should collect detailed exposure history for selected chemicals and work duration. Secondly, higher prevalence of occupational exposures in the main group may result from differential exposure classification bias, or recall bias, frequently reported from case-control studies of serious medical conditions and disease in children. This recall bias, if any, may produce high prevalence of exposure in cases and low prevalence of parental exposure in controls, yielding elevated ORs.

Our findings have a number of implications for prevention. Kazakhstan, in Soviet times, was a very developed industrial region, where groups of plants and factories in chemical, metallurgical or mining industries formed clusters, situated close to or within the large cities, such as Shymkent or Ust-Kamenogorsk. At present, most of that powerful industry has collapsed, leaving a few locations with populations exposed to hazardous substances in the workplace. Local population and workers are exposed to heavy metals, solvents, reactive chemicals, such as in the metallurgic industry in the East health effects of chemical exposure to metals is well documented, exposure levels may be quite high, as shown in studies from similar industries[10], however prevention programmes have not been targeted to reduce the burden for reproductive health, and a greater likelihood of CP in those exposed, as on the current study, has not received sufficient attention. Compliance with regulations remains understudied, and the true exposure levels of the working population remain very poorly documented.

Kazakhstan claimed transfer to cleaner and energy-efficient technologies in recent years, hosting Expo-2017, promoting wider implementation of green energy, but the size of population, still exposed to workplace hazards from older industries may still be very high. For environmental health science research, the nature of chemical exposure of those employed in hazardous workplaces in the country remains very poor characterized, since the access to employer's documentation is very limited. Workers are likely unaware of chemical exposure, therefore, family planning does not imply discussion on the potential risks from work. This study raises concern over the need to set up a system of educations for employees in the hazardous workplaces, as well as the need for counseling and informing primary care doctors managing young women in the reproductive age planning to have children in future.

This first presentation on the association of occupational chemical exposures of parents with CP in their children confirmed a few earlier presentations that father's exposure could increase the odds of the disease. The study uncovered the need for proactive counseling of parents about the risk, whereas the mitigation of chemical exposure of parents is proposed for the time of pregnancy planning.

Conclusions
Father's occupational chemical exposure increased the odds of CP in children (OR 18.7 (95% CI 3.3; 105.7), adjusted for age, sex, father's highest attained education and mother's education

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